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RESEARCH PAPER

Alternative Solvent-Free Preparation Methods for Felodipine Surface Solid Dispersions

J. Kerč,[1,*] S. Srčič,[2] and B. Kofler[1]

[1]*Lek Pharmaceutical and Chemical Company d.d., Research and Development Division, Celovška 135, 1526 Ljubljana, Slovenia*
[2]*University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia*

ABSTRACT

Surface solid dispersions were prepared via physical mixture and were either heated in a vacuum dryer or in a microwave oven for different periods of time. The physical state of felodipine in solid dispersions was studied using differential scanning calorimetry and x-ray powder diffractometry. USP paddle method was used for felodipine dissolution studies. The use of vacuum or microwave energy led to a significant improvement of felodipine dissolution which was caused partly by the amorphous state of felodipine and a large surface area of amorphous silicon dioxide.

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs has long been and still remains a problem to the pharmaceutical industry because the dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form. In this case, the physicochemical factors controlling the dissolution rate may be described by the Noyes–Whitney and Nernst equations (1,2). Dissolution rate is directly proportional to the surface area and can be increased by decreasing the particle size of the drug. Since simple micronization of the drug is usually followed by its aggregation, particle size reduction can be achieved by other techniques such as administration of eutectic mixture, coprecipitate, solid solution, surface solid dispersion, etc. (3–7).

Each of these approaches for altering the dissolution rate requires a unique type of drug molecule to exhibit its effect. Various water-insoluble drugs, such as solvent deposited on fumed silicon dioxide, have been reported to have higher dissolution rates than the pure micronized

*To whom correspondence should be addressed.

drugs. Surface area of the silica gel adsorbents was a controlling factor of the increased dissolution rate of the adsorbate samples (8).

A solvent deposition system is a solid dispersion in which a drug is deposited from a solvent on the surface of a carrier. This step is usually done by evaporation of the solvent used for distribution of the drug onto the matrix. The choice of solvent or mixed solvent system, and the rate and the completeness of its removal are critical to the quality of the dispersion. The environmental problems of the use of organic solvents must also be considered.

In addition to solvent deposition systems a melting method is also often used for solid dispersion preparation. The use of a temperature above the melting point of the drug during the fusion process is often a great disadvantage of this method because many drugs undergo some or complete decomposition at melting point.

To achieve the change of the crystalline state of the drug in solid dispersion, microwave energy instead of the conventional heat can be satisfactorily employed.

In vacuum the drug seems to sublime from the crystals and immediately deposit on the carrier surface in the amorphous state (9). The properties of the carrier have a great influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of the drug: it should be freely water-soluble with intrinsic rapid dissolution properties, nontoxic and pharmacologically inert, soluble in a variety of solvents, chemically compatible with the drug, and should not form a strongly bonded complex with the drug.

The aim of this study was to investigate the effect of various preparation methods and the type of carrier on the state and dissolution profile of felodipine.

MATERIALS

Felodipine, a calcium antagonist from the group of dihydropyridine derivatives which is practically insoluble in water and has a low dissolution rate (10–12), was used as a model drug. Porous silicon dioxide KG 100 (Merck, Germany) as an amorphous and sodium chloride (Kemika, Croatia) as a crystalline carrier were used for felodipine surface solid dispersions.

METHODS

Surface Solid Dispersion Preparation

Surface solid dispersions containing 20% felodipine and 80% carrier were prepared via physical mixture. Both felodipine and the carrier were previously sieved through a 100-μm screen. The physical mixture was either heated in a vacuum dryer (ERT 21 AC, UNIS, Slovenia) at 100°C and $0.01 \cdot 10^5$ Pa or in a microwave oven (MR 5900, Hitachi, Japan) at maximal power (500 W) for different periods of time.

The solvent deposition method using methylenechloride as a solvent was employed as a reference method for preparation of surface solid dispersions.

Thermal Analysis

A DSC-4 differential scanning calorimetry (Perkin-Elmer, Norwalk, CT) was used to obtain DSC scans. The thermal behavior of felodipine and carriers was studied in a dynamic nitrogen atmosphere (50 ml/min) with a heating rate of 10 deg/min. The instrument was calibrated with 99.999% indium. Sample sizes were in the range of 1–2 mg of felodipine in the solid dispersion and were crimped in an aluminium pan. An empty crimped aluminium pan was used as a reference.

X-ray Diffraction (Guinier Powder Method)

X-ray diffraction patterns of powdered samples of a mixed particle size range, mounted on adhesive tape, were recorded using a Guinier de Wolff Camera, Model I (Enraf-Nonius, The Netherlands) with CuK_α (λ = 1.54056 Å) radiation and a crystal monochromator. The experiments were carried out at room temperature under the following conditions: voltage, 36 kV; current, 16 mA; exposure time, 1.5 hr. Evaluation of x-ray films was carried out using transmission densitometry.

Dissolution Studies

The dissolution studies of felodipine from powdered samples were conducted in distilled water at 37°C. The USP paddle method was used to determine the dissolution rate of the samples: 900 ml of dissolution medium, 37°C, 100 rpm.

Samples containing 10 mg of felodipine were weighed accurately and spread over the dissolution medium surface. Aliquots of dissolution medium were withdrawn periodically and passed through a 0.45-μm membrane filter. The absorbance was determined spectrophotometrically at 240 nm using a UV-VIS spectrometer (Perkin-Elmer). Immediately after aliquots of dissolution medium were withdrawn, equal aliquots were added to maintain a constant volume. Cumulative cor-

rections were made for previously withdrawn aliquots in calculating the amount of felodipine dissolved.

RESULTS AND DISCUSSION

Felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate), a calcium antagonist, is a member of dihydropyridine family in which analogs such as nifedipine, nicardipine, and amlodipine are found. It is practically water-insoluble. Its aqueous solubility has been determined to be 0.5 mg/l at ambient temperature (13) and 1.2 mg/l at 37°C (14), and reports on the solubility and dissolution rate enhancement have been published (4–6).

In this work an attempt was made to prepare solid dispersions at the temperature below the melting point of the drug and without using any solvent, of which complete removal is often a very critical step in solid dispersion preparation. Vacuum at 100°C as well as microwave energy were found to give surface solid dispersions with satisfactory physicochemical properties (15).

X-ray and DSC analyses of surface solid dispersions for which amorphous silicon dioxide KG 100 was used as a carrier showed that the crystalline structure of original felodipine changed to a microcrystalline or amorphous state in surface solid dispersions prepared in vacuum or in a microwave oven and in solvent deposit (Figs. 1 and 2). In vacuum felodipine seems to sublime

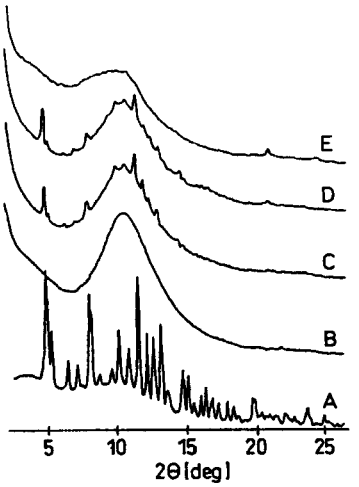

Figure 1. X-ray powder diffraction patterns of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100, vacuum; (c) 20% fel/KG 100, solvent deposit; (d) 20% fel/KG 100, physical mixture, ambient temperature; (e) KG 100.

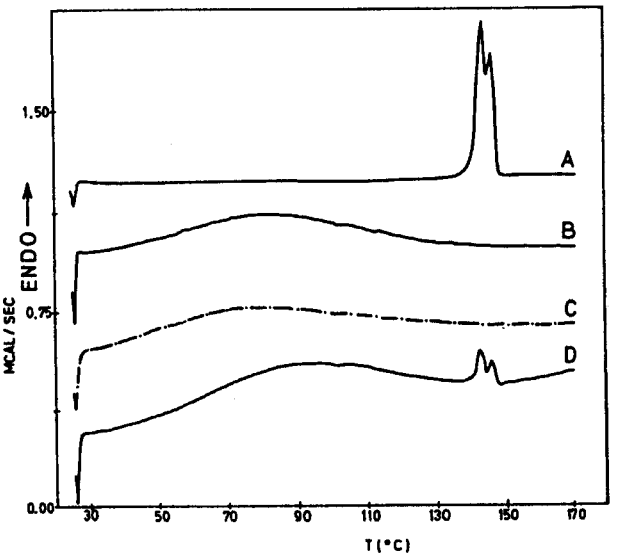

Figure 2. DSC scans of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100 vacuum; and (c) 20% fel/KG 100, solvent deposit; (d) 20% fel/KG 100, physical mixture, ambient temperature.

from the crystals and immediately deposit on the carrier surface in the amorphous state (9). The results of dissolution studies showed that the dissolution rate of felodipine from solvent deposit as well as vacuum-prepared surface solid dispersions increased markedly as compared to the dissolution rate of felodipine alone, and also increased in comparison to the dissolution rate of ambient-temperature-prepared physical mixture (Fig. 3).

The reduction in particle size and the increase in the specific surface area improved the dissolution of felodipine from surface solid dispersion up to 10-fold.

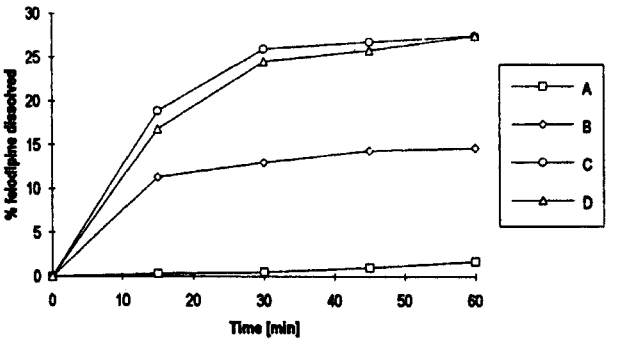

Figure 3. Dissolution profiles of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100, physical mixture, ambient temperature; (c) 20% fel/KG 100, vacuum; (d) 20% fel/KG 100, solvent deposit.

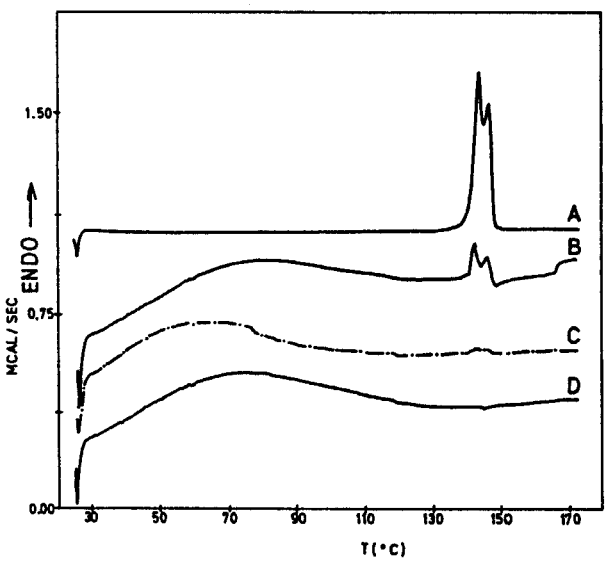

Figure 4. DSC scans of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100, microwave, 5 min; (c) 20% fel/KG 100, microwave, 10 min; (d) 20% fel/KG 100, microwave, 15 min.

DSC scans of felodipine/KG 100 surface solid dispersions showed that the melting peak of felodipine gradually vanishes when the time of exposure of the physical mixture to microwave energy increases from 5 to 15 min (Fig. 4).

Accordingly, x-ray analysis confirmed the amorphous state of felodipine in felodipine/KG 100 surface solid dispersions (Fig. 5). The time of exposure of the sample

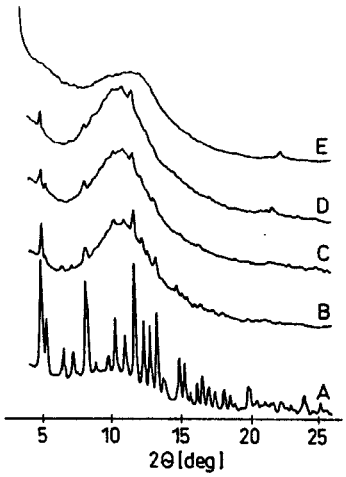

Figure 5. X-ray powder diffraction patterns of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100, microwave, 5 min; (c) 20% fel/KG 100, microwave, 10 min; (d) 20% fel/KG 100, microwave, 15 min; (e) KG 100.

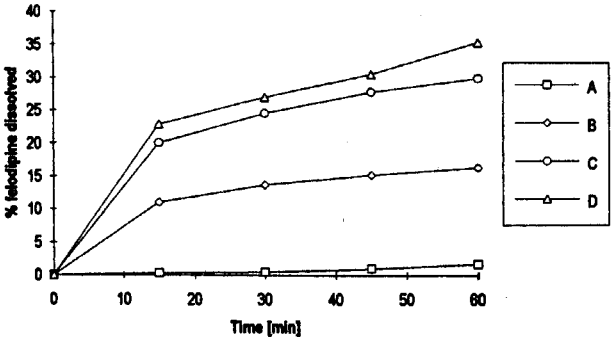

Figure 6. Dissolution profiles of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/KG 100, microwave, 5 min; (c) 20% fel/KG 100, microwave, 10 min; (d) 20% fel/KG 100, microwave, 15 min.

to microwave energy was found to have an important effect on the amorphous state of the drug and its dissolution rate, respectively (Fig. 6).

Solvent deposition or vacuum-prepared surface solid dispersion using sodium chloride as a crystalline carrier caused a minor change in the crystallinity of felodipine. A transition of two polymorphic forms present in original felodipine to mostly one polymorphic form is evident from DSC scans (Fig. 7).

X-ray analysis showed that felodipine in surface solid dispersions with sodium chloride exposed to microwave

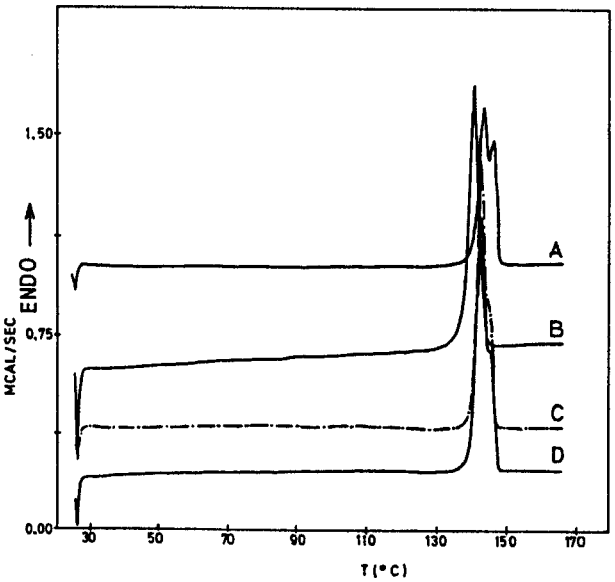

Figure 7. DSC scans of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/NaCl, solvent deposit; (c) 20% fel/NaCl, vacuum; (d) 20% fel/NaCl, physical mixture, ambient temperature.

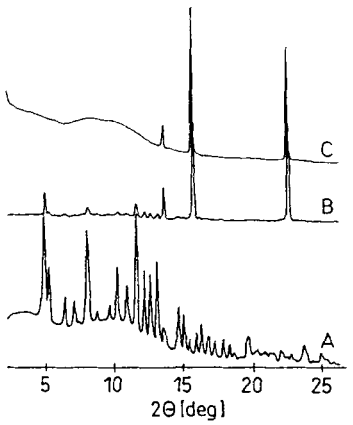

Figure 8. X-ray powder diffraction patterns of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/NaCl, microwave, 15 min; (c) NaCl.

energy changed to an amorphous or microcrystalline state (Fig. 8), but the DSC analysis glass transition point at 45°C was determined and glassy state of felodipine was confirmed. On heating the sample in DSC apparatus, sodium chloride accelerated the crystallization of amorphous glassy felodipine in solid dispersion which

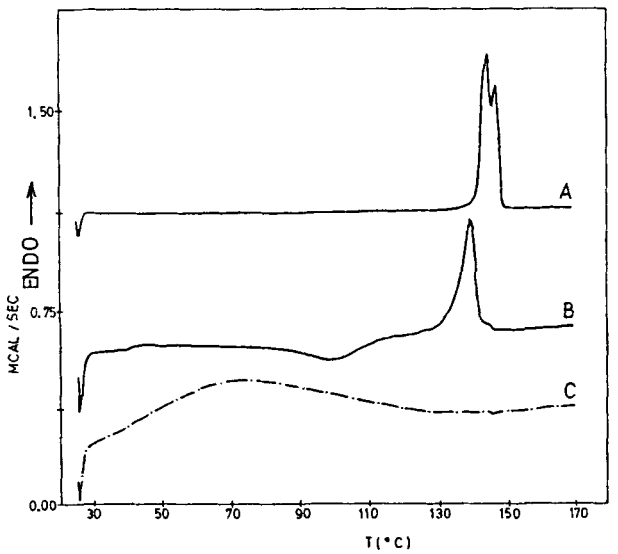

Figure 9. DSC scans of felodipine surface solid dispersions: (a) felodipine; (b) 20% fel/NaCl, microwave, 15 min; (c) 20% fel/KG 100, microwave, 15 min.

is shown by a broad exotherm with a minimum at 100°C (Fig. 9) and was found to be a less suitable carrier for surface solid dispersions.

CONCLUSIONS

Heating the material below melting point in a vacuum dryer or using microwave energy proved to be a successful preparation method for felodipine surface solid dispersions. The amorphous state of felodipine in surface solid dispersions was proved using DSC and x-ray powder diffractometry. Since no organic solvent was used in surface solid dispersion preparation (a vacuum or microwave oven were used to achieve the same form and dissolution characteristics of felodipine), these two methods are preferred to the solvent deposition method.

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